Ashdin Publishing
Journal of Drug and Alcohol Research
Vol. 14 (2025), Article ID 166605, 6 pages
DOI: 10.4303/JDAR/236451

Research Article

Development and Evaluation of Stable Minitablets Containing Suvorexant Infused Self-Emulsifying Drug Delivery Systems

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Received: 10 June 2025; Manuscript No: JDAR-25-166605; **Editor assigned:** 12 June 2025; PreQC No: JDAR-25-166605 (PQ); **Reviewed:** 26 June 2025; QC No: JDAR-25-166605; **Revised:** 11 July 2025; Manuscript No: JDAR-25-166605 (R); **Published:** 19 July 2025; DOI: 10.4303/JDAR/236451

Abstract

The present study proposes to prepare minitablets where Suvorexant-loaded Self-Emulsifying Drug Delivery Systems (SEDDS) will be employed to overcome its poor solubility in water and achieve an increased oral bioavailability. The testing of different types of liquid excipients (lipid-based) including Transcutol HP, Tween 80, Acconon, and Labrasol ALF were tested in terms of their solubilisation properties. The optimised Self-Emulsifying Drug Delivery Systems (SEDDS) with composition of Transcutol HP (30 v/v), Tween 80 (45 v/v), Acconon (20v/v) and Labrasol ALF (5v/v) had a desirable emulsification time, average drop size of about 130 nm and good release of the drug in media approved by the USFDA. To provide a solid SEDDS, formulations were adsorbed to porous and non-porous carriers alike and then compressed down to minitablets. Characterisation included in vitro release studies, flow studies, and Pharmacokinetic studies in rats. Solid and liquid SEDDS showed a significant increase in Cmax and AUC compared to the reference marketed product and solid minitablets were a predictable and effective dosage form in the delivery of Suvorexant.

Keywords: Suvorexant; Self-Emulsifying Drug Delivery Systems (SEDDS); Minitablets; Dissolution; Bioavailability

Introduction

Suvorexant is a dual orexin antagonist and is used in treating insomnia. The oral administration of the compound in the form of oral intake of the compound has however been challenged by its limited water solubility and strong affinity to lipids. This results in inconsistent absorption and supply in the body. In a growing number of cases, Self-Emulsifying Drug Delivery Systems (SEDDS) are recognised as powerful methods of reducing the water-insolubility of poorly aqueous soluble pharmaceutical molecules [1-3]. Against this background, an invention in the form of the formulation and testing of strong minitablets with Suvorexant-filled Self-Emulsifying Drug Delivery Systems (SEDDS) constitutes a new step towards the improvement of drug delivery efficiency and clinical outcomes. The introduction describes the reasons of using SEDDS (Self-Emulsifying Drug Delivery Systems) to deliver Suvorexant and suggest the idea of stable minitablets as a solution to its poor administration by mouth. The study aims at showing that the Suvorexant-loaded SEDDS minitablets used as a pharmaceutical formulation could be very feasible and beneficial in enhancing the treatment of insomnia. The full evaluation of the developed product will be comprised, involving the evaluation of physicochemical properties of the product, conducting the in vitro dissolution, and stability assessment. Development of Suvorexant-loaded Self-Emulsifying Drug Delivery Systems (SEDDS) is an important approach to counter the problem of poor water solubility and variable bioavailability of Suvorexant. The current research involves an extensive strategy as it will commence with an investigation on the solubility of Suvorexant in diverse oil-based materials, including oils, surfactants, and cosurfactants. The use of pseudo ternary phase diagrams [4-7] can be used to determine the self-emulsion zone and accordingly presence of Self-Emulsifying Drug Delivery System (SEDDs) can be formulated. Here it is achieved by mixing of oil, surfactant and the cosurfactant at varying proportions. The process of optimisation is characterised by the repeatable and systematic approach in order to reach a well-defined and simple to understand SEDD system. Tests that can be conducted in regard to analyzing the improved formulation involve the analysis of the globule size, finding the zeta potential, analyzing the time necessary to achieve self-emulsification as well as conducting release and dissolution tests under different types of buffers, such as those indicated by USP as dissolution media. Secondly, the study broadens itself to the study of the creation of very efficient Self-Emulsifying Drug Delivery Systems (SEDDs) by adding the liquid SEDDs to the different carriers [8-13]. There is a series of the comparative analysis of the flow properties of the specified goals to select the most effective powder composition. Finally, the powder SEDDs will change into minimized tablets, and the form of the dosage will be stabilized and convenient due to oral delivery of Suvorexant. The study intends to come up with a valid and efficient pharmaceutical formulation that can enhance therapeutic efficacy of Suvorexant in treating insomnia. This will be achieved by having systematic development and analysis process.

Materials and Methods

RIA international is in India, which supplied the substance Suvorexant. Lipid excipient was received as a source of Gattefosse, Abitec Corporation, and Sigma- Aldrich. The mesoporous silica is called Syloid 3645 XDP, which is a Hyderabad based W.R. Grace Company.

Study of solubility

The excess of Suvorexant was added to 1 mL various oils, surfactants, and cosurfactants and then incubated at 37°C in a time scale of 48 h. Drug content was analyzed using HPLC after the procedures of centrifugating and filtering.

The High-Performance Liquid Chromatography (HPLC) Examination Solvent phase: Methanol composition: 1 percent orthophosphoric acid in a 70:30 ratio, the flow rate was adjusted at 1.0 mL/min, column specifications: HSS C18; 4.6 150 mm.

Plotting of phase diagrams

The emulsionization territory was determined by ternary phase diagrams development with the application of SigmaPlot [13,15]. Various combinations of ratio towards Transcutol HP, Tween 80, Acconon, and Labrasol ALF were tested (Figure 1- Figure 7).

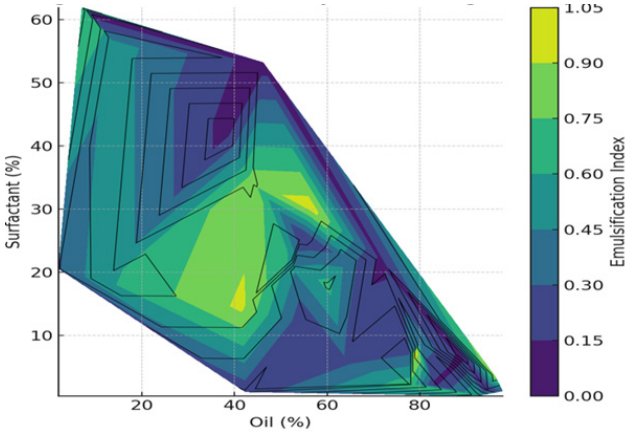
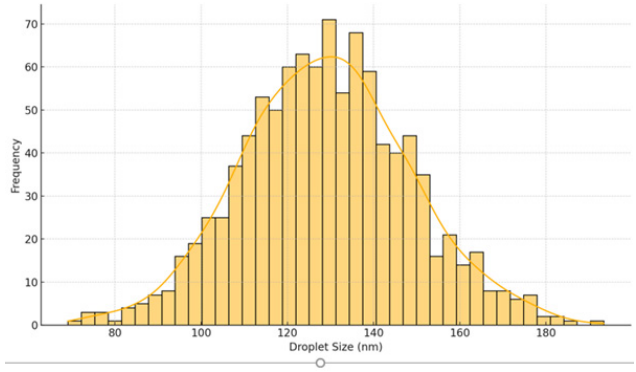


Figure 1: Pseudo ternary phase diagram showing the self-emulsifying region of blank SEDDS formulations.



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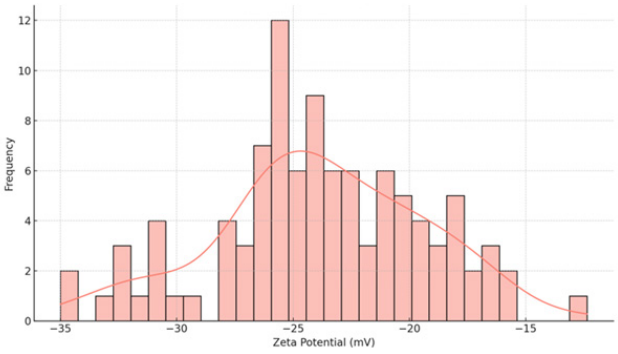


Figure 3: Zeta potential of optimized SEDDS formulation.

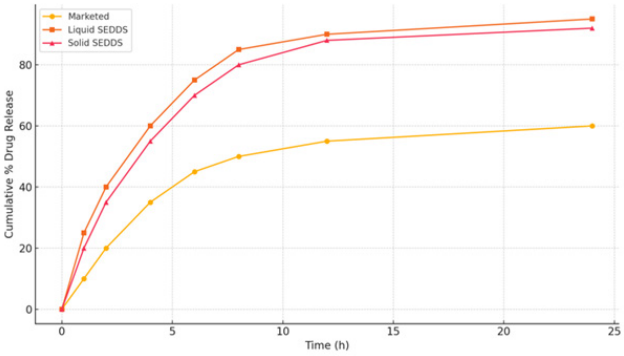


Figure 4: *Invitro* drug release profiles of Suvorexant liquid SEDD, solid SEDD and market product.

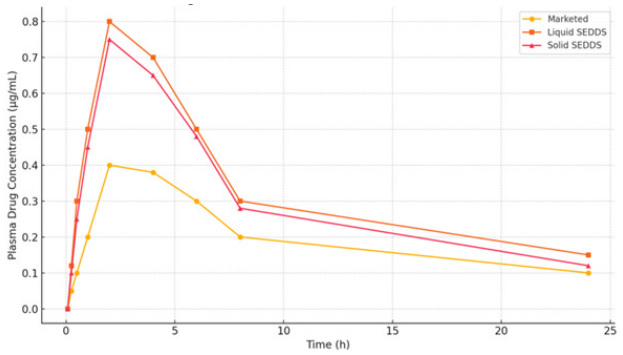


Figure 5: *In vivo* plasma drug concentrations at different time intervals.

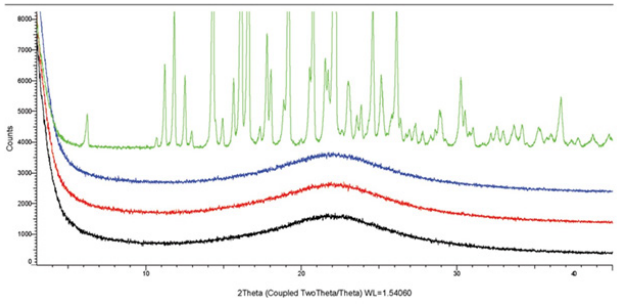
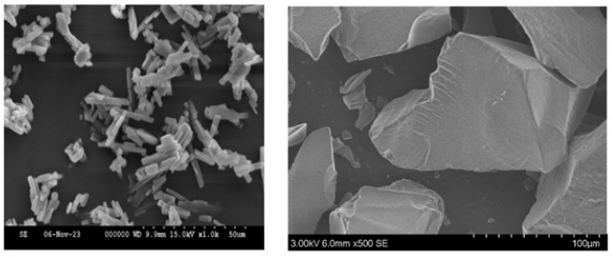


Figure 6: Xray diffractograms of Suvorexant active in comparison to physical mixtures and carrier loaded (Porous and non-porous) solid SEDDs.



Suvorexant active Suvorexant loaded Syloid®XDP

Figure 7: Scanning electron micrographs of plain Suvorexant and Suvorexant loaded Syloid®XDP.

In vitro dissolution study

Drug release was determined with the help of USP Apparatus I (Basket) under Rotation speed of 75 rpm within 900 mL volume with 0.4% SLS.

Preparation of drug loaded solid SEDDs

The straightforward beaker and a glass rod and the burette were employed to make up the solid formulations of SEDDs. The liquid SEDDs was added drop wise along with continuous stirring up until complete adsorption took place to obtain a free-flowing powder. The SEDDs whose formulations are robust were further characterised to analyse their morphology and flow characteristics.

Flow property evaluation

Characterization of solid SEDDS was characterized by "bulk density, tapped density, Carr Index, and the Hausner ratio". Table 1 contains the flow data.

Table 1: Flow behavior of liqui-solid powders prepared using porous and non-porous carriers.

Carrier	Weight of carrier	Weight of L – SEDD			
		0.5	1	1.5	2
Syloid® XDP	1	Free flow	Free flow	Free flow	Lump
Mg.Al Silicate	1	Free flow	Free flow	Wet mass	-
MCC 102	1	Free flow	Lump	Lump	-

Pharmacokinetic studies

After receiving approval of IAEC, oral administration of Suvorexant formulation was applied to groups of male Sprague-Dawley rats (n12) and this was decided in three groups. In group 1, all the rats were gavage administered. Group 2 and 3 creatures were administered with both their treatment *via* the oral route in form of capsules. "The samples of blood were collected with the help of cannulation by means of jugular vein at the following time points: 0.08, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours following the dosing." This yielded nine time points to the group each of which having four rats sampled. The samples of blood were centrifuged and thus the extraction of plasma occurred. The analysis of Suvorexant in plasma samples taken by Groups 1, 2, and 3 was performed with the help of the specific LC-MS/MS bioanalysis tool adapted to this task. Pharmacokinetic parameters in plasma Suvorexant were calculated on a basis of standard non-compartmental analysis using Phoenix 8.3 (Certara) based on pharmacokinetic software. The trapezoidal analysis used was the linear trapezoidal, as well as the linear interpolation (Table 2).

Table 2: Physical behavior of liqui-solid powders prepared using porous and non-porous carriers.

Ingredients	Formulation - I	Formulation - II	Formulation - III
	(Syloid® XDP)	(Mg. Al Silicate)	(MCC)
Suvorexant	10	10	10
Transcutol HP	60	60	60
Tween 80	90	90	90
Acconon	40	40	40
Oil loading ratio	01:01.5	01:01.1	01:00.3
Carr's Index	19	24	40.3
Hausner ratio	1.23	1.3	1.76
Flow	fair	Passable	passable
Powder weight / capsule (mg)	333	382	800
Capsule size	small	Medium	bigger
Minitablets weight /capsule (mg)	430	575	635
Friability	0.31	0.53	0.22
Content uniformity	100.4	98.9	98.3

Table 3: Pharmacokinetic parameters of Suvorexant in Rats after oral administration of Suvorexant Market product Vs optimized SEDDs formulations (liquid and solid).

Parameters	Suvorexant (Market)	Optimized liquid SEDD	Solid SEDD prepared with Syloid®XDP
T_{max} (h)	1.20 ± 0.42	0.50 ± 0.64	0.65 ± 0.82
C_{max} (µg/ml)	0.416 ± 0.34	0.862 ± 0.87	0.781 ± 0.56
$AUC_{0-\infty}$(h.µg/ml)	2.71+1.20	8.77+2.02	7.63+0.68
k_{el} (h^{-1})	0.07 ± 0.05	0.09 ± 0.07	0.1 ± 0.03
$t_{1/2}$ (h)	9.76 ± 2.89	6.89 ± 1.88	7.68 ± 6.34

Note: Each value represents the mean ± S.D. (N=4); SEDDS (Self-Emulsifying Drug Delivery Systems), C max maximum concentration in the blood; Tmax time for the occurrence of Cmax , AUC area *p< 0.05 compared with suvorexant powder, **p<0.05 compared with liquid SEDDs"under the curve, kel elimination rate constant, t1/2 elimination half life.

Statistical analysis

The Statistical significance was tested using Student t-test.

Results and Discussion

In order to obtain maximum drug loading as well as minimizing the final dosing volume, a range of components was checked with regard to their solubilizing ability. Transcutol, among other lipid excipients that were tested to check on the suvorexant solubility, had the highest solubility of 100

mg/ml with the HLB of 4.2. This was followed by Capmul MCM and Capryol 90 that were classified as oils. Furthermore, a number of other surfactants such as Acconon (HLB 4.9), Labrasol ALF (HLB 13.7) and Tween 80 (HLB 15) were found to be favorable in solubility of the suvorexant and used together to prepare the SEDDs.

It was designed to come up with a set of SEDD formulations and test their ability to self-emulsify by visual observation. The drug was not used to generate a pseudo ternary phase diagram in order to identify self-emulsifying region and to optimise oil, surfactant and cosurfactant concentrations. The phase diagram displayed in Figure 1 corresponds to the system with Transcutol, Labrasol ALF, and Acconon as cosurfactants.

Bearing in mind that droplet size is one of the most crucial parameters in the SEDD systems, it was a critical aspect of formulation optimisation. Their observations indicated that as the concentration of the surfactant was increased the size of the drop formed by the particles decreased. The combination of Acconon and Labrasol ALF containing different cosurfactants were important in the development of effective self-emulsifying systems, which were used in a particular ratio of 4:1.

The Powder X-ray Diffraction (PXRD) patterns presented in Figure 6 depict peculiarities of suvorexant and solid Self-Emulsifying Drug Delivery Systems (SEDDs). The crystalline property of Suvorexant exhibits various peaks at distinct angles whereas the solid SEDDs lack intrinsic peaks, which indicate that the medicine can be effectively transformed into the amorphous constitution.

Moreover, Figure 6 provides the Scanning Electron Microscopy (SEM) pictures, which show the pure drug together with solid SEDDs. The SEM analysis reveals that suvorexant appears in the form of different crystals with smooth surface and amorphous silica gel particles has highly porous surfaces. The improved solid SEDDs show a smooth surface of the particle without any crystalline structure which means that an adsorption of the amorphous suvorexant product was performed in the porous structure of the mesoporous silica gel.

Both solid and liquid "Self-Emulsifying Drug Delivery Systems (SEDDs) were investigated in vitro in terms of drug release and compared to a commercially available product applying the medium recommended by the USP (see Figure 4). These results show that the rate of release of the drug in the commercially available formulation is almost 50 times lower in comparison to the respective releases of liquid and the solid SEDDs." The release profiles of both the liquid and the solid SEDDs are virtually identical, which points into the fact that the carrier does not have any effect on the release properties of suvorexant [16,17].

As shown in figure 5, the concentration-time curves of the marketed product of suvorexant and the liquid and solid formulations of suvorexant SEDD combine were compared. The results mean that the commercial product demonstrates the lowest mean plasma concentration of suvorexant compared to liquid and solid SEDDs and this can be explained by its poor solubility and dissolution rate. Both liquid and solid SEDD s indicate faster release patterns compared to the commercial product, their consequent monographs almost overlapped, indicating that the adsorbent has no interference effect on the release of suvorexant in vivo.

Table 1 gives an overview of the Pharmacokinetic parameter package of suvorexant formulations. The values of Area Under the Curve (AUC) and peak concentration (Cmax) were significantly higher in the liquid and solid SEDD formulation than the marketed formulation ($p << 0.05$). Liquid SEDD AUC 0- infinity and Cmax were decreased by approximately four and two times when compared to suvorexant approved in the market, respectively. Similar tendencies were observed in the solid SEDD formulations.

They measured the flow properties of solid powder Self Emulsifying Drug Delivery Systems (SEDDs), and their attention was paid to such characteristics as bulk density, tapped density, or Carr index [18-20]. Formulae prepared using Syloid XDP showed an increased fluidity when compared to formulation prepared using MCC 102 and dicalcium phosphate. Out of the carriers assessed, Syloid XDP had shown extraordinary liquid absorbency capacity where one gramme can absorb 150 per cent of its weight in a liquid maintaining a free-flowing characteristic. On the other hand, the other two non-porous carriers became free-flowing powder only at the ratio of 1: 0.5 and this really goes towards importing the better absorbance capacity of mesoporous silica gel. After this, compression of the powders using appropriate tooling was carried out to form minitablets.

Conclusion

This study managed to formulate and appraise an excellent minitablet composition of Suvorexant using Self-Emulsifying Drug Delivery Systems (SEDDS). The development process was initiated with the preparation of liquid Self-Emulsifying Drug Delivery Systems (SEDDs) whose development necessitated an extensive study of solubility using different lipidic excipients. Thereafter, pseudo ternary phase diagrams were prepared to determine the regions where self-emulsion occurs." Finally, SEDDs have been created with the help of the trial-and-error approach with the proportions of oil, surfactant, and cosurfactant being refined. Using the specific method of doing so we have managed to produce a system that is as simple and clear as possible, and which has the highly desirable quality of being self-emulsifying.

The analysis of modified liquid SEDD formulation showed that it had the optimum dimension and charge of globules, faster self-emulsifying time and increased release/dissolution properties in different solutions like 0.1N H Cl, phosphate buffer at PH 6.8 and biorelevant media. These prop-

erties were essential towards successful administration and uptake of the drug. A change of liquid SEDDs into solid state requires addition of liquid formulations to carrier materials, which leads to a formation of powders with both good flow properties owing to evaluations of both bulk density and tapped density, Carr index and Hausner ratio. The selected powder SEDD could consequently be produced into minitablets, a new, drug form with advantages of SEDDs, but with the ease of administration of solids and the stability of tablet dosage forms.

Pharmacokinetics studies have revealed that it is indeed considered that the minitablet version of Suvorexant will have a higher absorption, thus resulting to a better bioavailability. The stability ascertained at the accelerated tests confirmed the stability of the formulation satisfying the integrity and the therapeutic efficacy of the formulation with time.

The use of advanced techniques of characterisation "such as Differential Scanning Calorimetry (DSC), X-Ray Diffraction (XRD), and Scanning Electron Microscopy (SEM)" allowed gaining positive information regarding the physicochemical transformations of Suvorexant. The reorganization of Suvorexant, as a crystalline to an amorphous form was confirmed by application of these techniques and this is in essence the reason behind the observed improvements in solubility as well as bioavailability.

The described study is novel and useful in the administration of medications with low-water solubility such as Suvorexant. It also sets a reference to the discovery of hard Self-Emulsifying Drug Delivery Systems (SEDDs) and the transformation to a dispatchable hands-on minitablet state to be used by the patient. In further research, researchers should also conduct some clinical trials to determine the safety and efficacy of these minitablets in humans. This research should aim at unlocking the potential of these minitablets in enhancing the therapeutic effects as well as augmenting patient compliance to a wider variety lipophilic drugs.

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